Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee
July 28, 2009

Location: Hilton Washington DC/Silver Spring, Maryland Ballroom,
8727 Colesville Road, Silver Spring, MD.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the July 28, 2009 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on September 4, 2009.

I certify that I attended the July 28, 2009 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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Elaine Ferguson, M.S.,R.Ph.
Designated Federal Official

Robert Harrington, M.D. F.A.C.C.
Committee Chair

Meeting of the Cardiovascular and Renal Drugs Advisory Committee
July 28, 2009

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac

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The Cardiovascular and Renal Drugs Advisory Committee, Center for Drug Evaluation and Research met on July 28, 2009 at the Hilton Washington DC/Silver Spring, Maryland Ballroom, 8727 Colesville Road, Silver Spring, MD. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. This was a voting meeting. There were approximately thirty (30) persons in attendance.

Issue: The committee discussed new drug application (NDA) 22–449 binodenoson injectable, lyophilized solid 250 micrograms vial, King Pharmaceuticals Research and Development, Inc., for the proposed indication: Short acting coronary vasodilator for use as an adjunct to noninvasive myocardial perfusion imaging tests to detect perfusion abnormalities in patients with known or suspected coronary artery disease.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
Robert A. Harrington, M.D., F.A.C.C. (Chair), Henry R. Black, M.D. , Jonathan L. Halperin, M.D., Sanjay Kaul, M.D. , Mori J. Krantz, M.D., F.A.C.C., Darren K. McGuire, M.D., M.H.Sc., James D. Neaton, Ph.D., Emil P. Paganini, M.D., F.A.C.P., F.R.C.P.,

Special Government Employee Consultants (Voting):
Frank M. Bengel, M.D., Lyle D. Bromeling, Ph.D., Peter Conti, M.D., Ph.D., Michael Domanski, M.D., Ph.D., John M. Flack, M.D., M.P.H., F.A.H.A. Sebastian G. Schneeweiss, M.D., Sc.D., James L. Tatum, M.D., Neil J. Weissman, M.D.

Industry Representative Members Present (Non-Voting):
Jonathan C Fox, MD, PhD, FACC

Guest Speaker (Non-Voting): None

FDA Participants (Non-Voting): Ellis Unger, M.D., Dwaine Rieves, M.D., Libero Marzella, M.D., Mark Levenson, Ph.D.

Acting Designated Federal Official:
Elaine Ferguson, M.S.

Open Public Hearing Speakers: None

The agenda was as follows:

8:00 a.m.	Call to Order Introduction of Committee	Robert Harrington, M.D. Chair, CRDAC
	Conflict of Interest Statement	Elaine Ferguson, M.S. Designated Federal Official, CRDAC
8:10 a.m.	FDA Opening Remarks	Rafel (Dwaine) Rieves, M.D. Director Division of Medical Imaging and Hematology Products, CDER, OND, OODP
8:20 a.m.	Sponsor Presentations: Introduction	Eric G Carter, PhD, MD Chief Science Officer, King Pharmaceuticals, Inc.
	Binodenoson Clinical Development Program	James E Udelson, MD Chief, Division of Cardiology, Tufts Medical Center
	Phase 3 Statistical Considerations	Lisa M LaVange, PhD Director of the Collaborative Studies Coordinating Center and Professor of Biostatistics, University of North Carolina at Chapel Hill
	Clinical Efficacy Results of Pivotal Phase 3 Trials	James E Udelson, MD Chief, Division of Cardiology, Tufts Medical Center
	Safety and Tolerability Assessment of Binodenoson	James E Udelson, MD Chief, Division of Cardiology, Tufts Medical Center
	Benefit Risk of Binodenoson	Eric G Carter, PhD, MD Chief Science Officer, King Pharmaceuticals, Inc.
10:05 a.m.	Break	
10:15 a.m.	Questions to the Sponsor	
10:45 a.m.	Clinical Summary of Safety and Efficacy Data	Libero Marzella, M.D., Ph.D. Medical Team Leader, Division of Medical Imaging and Hematology Products, CDER, OND, OODP
11:05 a.m.	Statistical Summary of Efficacy Data	Mark Levenson, Ph.D., Statistical Reviewer, Division of Biometrics, CDER, OTS
11:30 a.m.	Questions to presenters	
Noon	Lunch	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	Discussion of questions to committee	
3:30 p.m.	Break	
3:45 p.m.	Discussion of questions to committee	
5:00 p.m.	Adjourn	

Questions to the Committee

Please refer to the transcript for additional details and comments.

1. (Discussion) The primary endpoints for Studies 302 and 305 were changed from a patient-level concordance of binodenoson and adenosine myocardial perfusion images (MPIs) to a comparison of *average* summed difference scores (SDSs). Do the revised endpoints provide a robust measure of agreement between binodenoson and adenosine MPI?

   The committee generally did not regard the revised endpoints as an improved measure of agreement, compared to the originally proposed measure. However, the committee members expressed the opinion that it was reasonable for the analysis plan to be changed as more knowledge became available prior to the data unblinding.

2. (Discussion) All three phase 3 studies failed to achieve success upon the "original" primary endpoint of MPI *concordance*. However, success was achieved upon the "revised" endpoint of comparisons of *average* SDSs. Does this inconsistency impact your assessment of the agreement between binodenoson and adenosine MPIs?

   The committee generally thought the response to item 1 also addressed this topic. As noted above, the alteration in the endpoints, per se, was not of particular concern since it was performed prior to data unblinding. However, concerns were expressed about the uncertainty of "agreement" evidenced in the analyses.

3. (Discussion) Knowledge of MPI results may have impacted the decision to perform coronary arteriography in the phase 3 study population; ~ 16% of the population underwent the procedure. How useful are the coronary arteriographic images as a "truth standard" for establishing binodenoson-based MPI performance characteristics?

   Not very useful because of verification bias introduced by the influence of the MPI test on the decision to proceed to the truth standard test

4. (Vote) Do the phase 3 study results establish high binodenoson and adenosine MPI agreement?

   Yes = 5
   No = 11

   a. If you voted "yes," discuss the aspects of the results that most impacted your opinion.

      Most members stated that it was the sum of the multiple analyses, the potential for additional analyses to provide better evidence of agreement between the test agent and the reference agent and the safety profile.

   b. If you voted "no," discuss the types of data essential to establish high MPI agreement, including any important study design considerations.

      Many members stated that there need to be additional study(ies) of of adenosine test-retest variability) and verification of agreement between binodenoson-based images and adenosine-based images.

      A few members expressed that additional data may not be necessary, that additional analyses of the available data may help to characterize the test-retest variability.

      A few members questioned the justification for the equivalency bounds in the sponsor's non-inferiority comparisons of the study results.